Claim Rejections/Objections Withdrawn

The Examiner withdrew the objection to claim 54 as depending from a non-elected claim in response to applicants' cancellation of claim 54.

The Examiner withdrew the rejection of claim 48 under 35 U.S.C. §112, first paragraph.

The Examiner withdrew the rejection of claim 50 under 35 U.S.C. §112, second paragraph.

Objection to the Title

The Examiner maintained the objection to the use of the word "novel" in the title.

In reply, without conceding the correctness of the Examiner's position, applicants have amended the title to delete the word "novel."

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 47, 49-52 and 55-68 under 35 U.S.C. §112, first paragraph as lacking enablement commensurate with the scope of the claims. On page 3 of the Office Action, the Examiner stated that he agrees that the specification is generally enabling

for inhibition of inflammation by inhibition of RAGE/EN-RAGE interactions using anti-EN-RAGE, anti-RAGE, or s-RAGE. The Examiner further agreed that the specification is enabling for methods using anti-RAGE and s-RAGE to inhibit inflammation by inhibiting RAGE/EN-RAGE interactions. The Examiner also agrees that vectors and viruses are recognized in the art. However, the Examiner stated that the claims are drawn to methods using any compound that interferes with binding between RAGE and EN-RAGE, including peptides and antibodies of unspecified specificity, as well as unspecified chemical compounds. The Examiner asserts that the specification discloses only antibodies, while the claims encompass all other inhibitors of RAGE/EN-RAGE interaction. The Examiner stated that there is no information as to the regions of either protein that are important for binding that would allow one of skill to determine what compounds might interfere with binding. The Examiner stated that "s-RAGE" is merely the extracellular domain of RAGE and that there is no guidance as to what regions are important for the interaction with EN-RAGE and thus, allegedly no basis for the identification of any similarly-acting compounds. The Examiner stated that no "ligand-binding domain" of either protein is set forth in the specification. The Examiner stated that no possible targets for any other antibodies are specified. The Examiner took the position that it is not routine to screen large numbers of molecules, either peptides or small molecules, where the expectation of obtaining the desired activity is unpredictable. The Examiner concluded that without further guidance as to the structural and functional features of compounds

that would interfere with RAGE/EN-RAGE interactions, it would require undue experimentation for the skilled artisan to practice the invention as broadly claimed.

In reply, applicants respectfully traverse the rejection. Without conceding the correctness of the Examiner's position, applicants have amended claim 47 to recite a Markush group of compounds which the Examiner has agreed are enabled by the specification. See page 3 of the December 18, 2001 Office Action, lines 1-3. Applicants make this amendment without prejudice or disclaimer to their rights to pursue the subject matter of previous claim 47 in a future continuation or divisional application.

Claim 47 as amended is directed to a method for inhibiting inflammation in a subject which comprises administering to the subject a compound selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject. Claims 48, 49, 51 and 52 have been canceled without prejudice or disclaimer.

Thus, in view of this amendment, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claims 47, 49-52 and 55-68 as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated that the applicants have not set forth any defining characteristics of the molecules which are inhibitors of the RAGE/EN-RAGE interaction. The Examiner stated that no structural or functional features essential for the claimed function are described, nor are a representative number of members of the claimed genus of inhibitory molecules presented. The Examiner stated that no regions or characteristics of the either of the proteins important for the interaction, which would serve to identify a genus of inhibitors, are defined. The Examiner stated that no characteristics of antibodies other than anti-RAGE and anti-EN-RAGE are described. The Examiner stated that no features of any other type of inhibitor are described. The Examiner stated that no features of any other type of inhibitor are described. The Examiner stated that one skilled in the art would thus not conclude that applicant was in possession of the broadly claimed genus of compounds affecting RAGE/EN-RAGE interactions and thus methods of using these compounds.

In reply, applicants respectfully traverse the rejection and maintain that the presently claimed invention is sufficiently described in the subject specification in such a way as to reasonably convey to one of skill in the art that the inventors at the time the application was filed had possession of the claimed invention. Without conceding the correctness of the Examiner's position, applicants have amended without prejudice or disclaimer claim 47 and have canceled without prejudice or disclaimer claims 48-49 and 51-52.

Claim 47 as amended recites a method for inhibiting inflammation in a subject which comprises administering to the subject a compound selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject.

The Examiner has agreed that the specification provides sufficient written description for methods using anti-RAGE and anti-EN-RAGE (see Office Action, page 4, last three lines).

In view of this amendment, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 47-52 and 55-68 as indefinite under 35 U.S.C. §112, second paragraph. The Examiner stated that proteins and nucleic acids should be referred to by the identity number of an entered sequence in order to distinctly and unambiguously identify the protein.

In reply, applicants traverse the rejection. Claim 47 is amended and claims 48-49 and 51-52 are canceled without prejudice or disclaimer. The terms "RAGE" and "EN-RAGE" are clear and definite. On page 11, line 33 to page 12, line 22, the specification recites references to publications which include the exact sequences of human RAGE, V-domain of human RAGE. The sequence of bovine EN-RAGE is SEQ ID NO:1 in the subject specification. Applicants point out that claim 47 has been amended to refer to antibodies against RAGE and against EN-RAGE and to refer to soluble RAGE. Applicants also point out that the RAGE protein was isolated and named as shown in Neeper et al. (1992) and the EN-RAGE is named and described in the subject application, see Figure 5 and SEQ ID NO:1. Applicants submit that the use of the terms RAGE and EN-RAGE distinctly identifies the proteins. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 47-52, 55-68 as unpatentable over Hori et al. or Morser et al. in view of Ritthaler et al. The Examiner stated that the claims encompass s-RAGE and antibodies against RAGE. The Examiner stated that while the claims are drawn to methods of affecting RAGE/EN-RAGE interactions, this limitation is a limitation on the mechanism with no corresponding method step to achieve that limitation. The Examiner stated that s-RAGE and anti-RAGE antibodies are taught by Morser et al. and Hori et al., and involvement of RAGE in inflammation is taught by Ritthaler et al. The Examiner stated that Hori further teaches cytokine regulation of RAGE, particularly implicating TNF-alpha (p. 692) and specifically addresses atherosclerosis (p. 688). The Examiner stated that Morser et al. implicates the RAGE ligand AGE in inflammation (col. 1, lines 56-54). The Examiner stated that it would have been obvious to one of ordinary skill in the art to use s-RAGE or anti-RAGE to inhibit inflammation. The Examiner stated that one would have been motivated to do so because the role of RAGE in inflammation is taught by Ritthaler et al. The Examiner stated that the discovery of a novel mechanism does not render the method itself unobvious. The Examiner stated that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Morser et al. and Hori et al. with those of Ritthaler et al. to use s-RAGE or anti-RAGE to inhibit inflammation.

In reply, applicants traverse the rejection and maintain that the claimed invention is not rendered obvious by the combination of Hori et al. (8/95) or Morser et al. (U.S. Patent 4/96) in view of Ritthaler et al. (1995). Applicants claimed invention is directed to, *inter alia*, a method for inhibiting inflammation in a subject which comprises administering to the subject a compound selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject. Applicants submit that there is no motivation to combine the cited references and that, even if the references were combined, the combination does not render obvious the claimed invention.

Applicants emphasize that there is no motivation to combine Hori et al. with Ritthaler et al. Hori et al. merely provides general statements that RAGE ligands which are distinct from AGEs, might participate in "physiologic processes" other than diabetes. There is no mention of what these "physiologic processes" might be. See last sentence of abstract of Hori et al. which recites:

> These data indicate that RAGE has physiologically relevant ligands distinct from AGEs which are likely, via their interaction with the receptor, to participate in physiologic processes outside of the context of diabetes and accumulation of AGEs.

Hori et al. do not disclose or suggest a method for inhibiting inflammation in a subject as claimed in the subject application. The subtitle of the Hori et al. reference recites "Mediation of Neurite Outgrowth And Co-Expression of RAGE and Amphoterin In The Developing Nervous System." Hori et al. focus upon neurite outgrowth and development of the nervous system and there is no discussion or suggestion of inflammation. Hori et al. identify amphoterin as a ligand for RAGE and demonstrates that RAGE-amphoterin interaction promotes neurite outgrowth in cell culture. See page 25753, column 1, lines 10-30.

The Examiner states that the motivation to combine Hori et al. with Ritthaler et al. is "the role of RAGE in inflammation" as allegedly taught by Ritthaler et al. See page 6 of the Office Action, lines 4-6. On the contrary, applicants take the position that Ritthaler et al. do not teach or suggest a role of RAGE in inflammation. The term "inflammation" only appears once in Ritthaler et al., on page 688, column 2 with reference to a previous publication, i.e., Schmidt et al. (1993). Specifically, Ritthaler et al. state that "experimentally induced inflammatory lesions in response to local instillation of AGEs[12] showed prominent accumulation of cells strikingly positive for RAGE...." Schmidt et al. is reference number 12 as cited above, and is entitled "Regulation of Human Mononuclear Phagocyte Migration by Cell Surface-Binding Proteins for Advanced Glycation End Products" and was submitted as Exhibit 35 with the Information Disclosure Statement filed September 25, 2000. Schmidt et al. (1993) does not teach that RAGE has a role in

inflammation. Schmidt et al. identifies RAGE and the lactoferrin-like polypeptide AGE binding protein as having a role in mediating the effects of AGEs on mononuclear phagocytes. See page 2155, column 2. There is no teaching or suggestion by Ritthaler et al. of "the role of RAGE in inflammation." There is no motivation to combine Ritthaler et al. with either Hori et al. or Morser et al.

In Morser et al., the Examiner points to the statement that "evidence has indicated that the binding of AGEs to their receptors either directly or indirectly induces inflammatory responses in vessel walls..." in column 1, lines 56-60. There is no suggestion of the methods for treating inflammation as claimed presently in Morser et al. and Ritthaler et al. do not remedy this shortcoming. Morser et al. do not suggest administration of the claimed compounds in order to treat inflammation as presently claimed. There is no teaching or suggestion of the claimed methods in the combination of Morser et al. and Ritthaler et al.

Thus, in view of the amendments and remarks herein, applicants request that the Examiner reconsider and withdraw this ground of rejection and allow this application to pass to issue.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56 and §1.97 (a)-(c), applicants would like to direct the Examiner's attention to the following documents:

B

1. Morser et al. **PCT International Application No. PCT/EP97/01834**, filed April 11, 1997, published October 23, 1997; Publication No. WO 97/39125, Antibodies Against the Advanced Glycation Endproduct Receptor and Uses Thereof.

2. Morser et al. **PCT International Application No. PCT/EP97/01832**, filed 11 April 1997, published October 23, 1997, Publication No. WO 97/39121, Advanced Glycation Endproduct Receptor Peptides and Uses Thereof.

The above references are again listed on the PTO Form 1449 attached hereto as **Exhibit B.** Copies of the aforementioned documents are attached hereto as **Exhibits 1 and 2.** The Information Disclosure Statement fee of $180.00 is enclosed herewith. Applicants request that the Examiner make these documents of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

B

No fees, other than the $445.00 three-month extension of time fee and the $180.00 Information Disclosure Statement fee, are deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M. Love

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Jane M. Love 6/18/01

John P. White Date
Reg. No. 28,678
Jane M. Love
Reg. No. 42,812

John P. White
Registration No. 28,678
Jane M. Love
Registration No. 42,812
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

Exhibit A

--47.(2x amended) A method for inhibiting inflammation in a subject which comprises administering to the subject a compound [that interferes with the interaction between extracellular novel RAGE binding (EN-RAGE) peptide and receptor for advanced glycation endproduct (RAGE) in the subject] selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject.--

6